Donor Risk Index Has an Impact in Intraoperative Measure of Hepatic Artery Flow and in Clearance of Indocyanine Green: An Observational Cohort Study

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ABSTRACT

Background. The increase in indications for liver transplantation has led to acceptance of donors with expanded criteria. The donor risk index (DRI) was validated with the aim of being a predictive model of graft survival based on donor characteristics. Intraoperative arterial hepatic flow and indocyanine green clearance (plasma clearance rate of indocyanine green [ICG-PDR]) are easily measurable variables in the intraoperative period that may be influenced by graft quality. Our aim was to analyze the influence of DRI on intraoperative liver hemodynamic alterations and on intraoperative dynamic liver function testing (ICG-PDR).

Methods. This investigation was an observational study of a single-center cohort (n = 228) with prospective data collection and retrospective data analysis. Measurement of intraoperative flow was made with a VeriQ flowmeter based on measurement of transit time (MFTT). The ICG-PDR was obtained from all patients with a LiMON monitor (Pulsion Medical Systems AG, Munich, Germany). DRI was calculated using a previously validated formula. Normally distributed variables were compared using Student's *t* test. Otherwise, the Mann-Whitney *U* test or Kruskal-Wallis test was applied, depending on whether there were 2 or more comparable groups. The qualitative variables and risk measurements were analyzed using the chi-square test. $P < .05$ was considered statistically significant.

Results. DRI score (mean ± SD) was 1.58 ± 0.31. The group with DRI >1.7 (poor quality) had an intraoperative arterial flow of 234.2 ± 121.35 mL/min compared with the group having DRI < 1.7 (high quality), with an intraoperative arterial flow of 287.24 ± 156.84 mL/min ($P = .02$). The group with DRI >1.70 had an ICG-PDR of 14.75 ± 6.52%/min at 60 minutes after reperfusion compared to the group with DRI <1.70, with an ICG-PDR of 16.68 ± 6.47%/min at 60 minutes after reperfusion ($P = .09$).

Conclusion. Poor quality grafts have greater susceptibility to ischemia-reperfusion damage. Decreased intraoperative hepatic arterial flow may represent an increase in intrahepatic resistance early in the intraoperative period.

In an attempt to alleviate the shortage of liver grafts, the international transplant community has accepted the use of extended criteria organs [1]. These grafts tend to have worse

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outcomes in terms of graft survival, morbidity, and mortality. Primary nonfunction (PNF) is a serious complication, defined as patient death or graft loss in the first postoperative week in the absence of other causes of liver failure. The incidence of PNF has ranged from between 1.5% and 5% in various series [2]. Currently, there is much interest in identifying which kind of grafts are more susceptible to PNF in the postoperative period and how to treat or prevent use of such grafts. The donor risk index (DRI) is a scale validated by Feng et al that arose as an index of graft quality in long-term survival [3]. Indocyanine green clearance (ICG-PDR), assessed intraoperatively and on the first postoperative day, has shown power to predict mortality at 30 days. Moreover, measurement of hepatic artery flow (HAF) was shown to predict worse outcomes intraoperatively [4–6]. In this regard, graft quality, as defined by the DRI, could have an impact in these intraoperative measures.

MATERIALS AND METHODS

This was an observational study involving a single-center cohort of patients (n = 228), with prospective data collection and retrospective data analysis. It was carried out at the Liver Transplant Unit of Hospital General Universitario Gregorio Maranon, Madrid, Spain, a tertiary referral center. The study period was between January 2008 and December 2014. All patients provided informed consent before enrollment. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee. The recruited candidates were all adult patients who underwent complete orthotopic liver transplantation, including urgent transplants, cases of early retransplantation for PNF, and cases of late retransplantation. Cases were excluded when, due to technical problems, vascular flow could not be measured intraoperatively, or when there was early allograft dysfunction (EAD) secondary to acute vascular complications.

Measurement of Intraoperative Hepatic Flow

Intraoperative measurement was performed with a flowmeter (Medistin) based on measurement of transit time (MFTT) and Doppler technology. After performing vascular and biliary anastomosis at the end of the procedure, we sequentially measured the hepatic artery and portal flow just distal to the suture on the graft side. The absence of intraoperative blood flow or demonstration of very poor flow called for review of the arterial anastomosis, after verifying the absence of a compensatory effect of portal flow.

Indocyanine Green Clearance

A freshwater dilution of ICG monosodium salt was prepared at a concentration of 5 mg/mL. The PDR was obtained in all patients using either a LiMON monitor or $PiCCO_2$ monitor (Pulsion Medical Systems AG, Munich, Germany), which noninvasively measures ICG plasma concentrations by pulse spectrophotometry with a finger clip sensor that detects 4 near-infrared wavelengths. After intravenous injection of a bolus of the dye (0.5 mg/kg), ICG-PDR was calculated automatically according to the time course of the blood ICG concentration (normal value, 18%–25%/min) by monoexponential transformation of the original ICG concentration curve and backward extrapolation to timepoint zero (100%). Decay was described as percentage change over time (%/min). When reading the PDR was not possible (finger probe incorrectly placed or low finger perfusion associated with hypothermia, shock, or perfusion of high-dose noradrenaline), it was repeated after a 60-minute washout period (7% of cases). The ICG-PDR measurements were obtained 60 minutes after reperfusion intraoperatively and within the first 24 hours after the surgical procedure (PDR day 1), when hemodynamic stability was achieved and in the absence of transfusion or high-rate fluid infusion at the time of the measurement. A valid measurement of PDR was obtained for the 150 patients finally included in the study.

Surgical Technique

All patients underwent deceased donor liver transplantation (LT). Standard techniques were used with the piggyback technique, not with venovenous bypass. Anastomosis techniques related to the portal vein and hepatic artery were not modified.

Perioperative Variables

Donor data included age, cause of death, height, cold ischemia time, graft preservation solution (University of Wisconsin [UW] solution, histidine-tryptophan-ketoglutarate [HTK] solution, or Celsior), DRI, race, and graft allocation. The DRI was calculated using the formula described by Feng et al [3]. Donor standard total liver volume (sTLV) was calculated using the formula described by Vauthey et al [7].

Follow-up

Follow-up was started on the day of LT and was routinely performed at outpatient clinics. Patient follow-up was continued until August 1, 2015.

Statistical Analysis

The collected data were entered into a database created using SPSS version 20 for Macintosh. Quantitative variables are expressed as mean and standard deviation. If there was a normal data distribution (based on Kolmogorov-Smirnov test), the data were compared using Student's t test. Qualitative variables and risk measurement were analyzed using the chi-square test.

RESULTS

Donor and Recipient Characteristics

From January 1, 2008 to December 31, 2014, 228 adult liver transplants were performed at our center. The mean donor age was 51.45 (range, 16–85) years. The most common cause of death was cerebrovascular accident, followed by trauma and anoxia (78.08%, 14.9%, and 4.9%, respectively). The mean donor height was 67.17 cm. The mean cold ischemia time was 167.17 minutes. No non–heart-beating donor, split transplants were performed in the study period. Study demographics and characteristics are presented in Table 1.

The median DRI was 1.59 ± 0.31. The DRIs of the donors were calculated and divided into 2 categories: ≥1.70 ("low-quality grafts") and ≤1.70 ("high-quality grafts"). Table 2 shows donor demographics for low- and high-quality graft data.

Effect of DRI on Liver Blood Flow and ICG

The median hepatic artery flow was 265.29 ± 149.45 mL/min and the median ICG-PDR at 60 minutes was 15.76 ±

Table 1. Descriptive Statistics for Selected Donor and Recipient Parameters

Baseline Characteristics	
Donor age (years)	51.45 (9.92)
0–49	68 (29.8)
50–59	33 (14.5)
60–69	41 (18)
70–79	68 (29.8)
>80	18 (7.9)
Cold ischemia time (min)	478.58 (146.14)
Donor height (cm)	167.17 (10.1)
Cause of death	
Trauma	34 (14.9)
Stroke	178 (78.08)
Anoxia	10 (4.9)
Other	5 (2.19)
Etiology of liver diseases [number (%)]	
Viral cirrhosis	65 (33.3)
Hepatocellular carcinoma	95 (41.7)
Alcoholic cirrhosis	51 (26.2)
Fulminant hepatic failure	3 (1.3)
Primary biliary cirrhosis	5 (2.2)
Acute retransplantation	5 (2.2)
Chronic rejection	1 (0.4)
Sclerosing cholangitis	6 (2.6)
Cryptogenic cirrhosis	11 (4.8)
Hemochromatosis	1 (0.4)

Data expressed as mean (standard deviation) or frequency (%).

6.55%/min. Table 3 shows the relationships between hemodynamic hepatic blood flow and graft quality.

Hepatic artery flow (HAF) was significantly lower in the low-quality graft group (234.2 ± 121.35) than in the high-quality graft group (287.24 ± 156.84). Poor quality grafts had a high risk of having a HAF <180 mL/min (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.35–3.35; $P = .04$; Fig 1).

ICG-PDR was lower in the low-quality graft group (14.75 ± 6.52) than in the high-quality graft group (16.68 ± 6.47). The poorer quality grafts were at greater risk of having an ICG-PDR of <10.8%/min (OR, 2.15; 95% CI, 1.07–4.31, $P = .03$; Fig 2).

Table 2. Demographic Baseline Characteristics for Low- and High-quality Grafts

Baseline Characteristics	DRI >1.70 (n = 112)	DRI <1.70 (n = 116)
Donor age range (years)	71.56 (8.27)	47.66 (15.21)
0–49	3 (2.7)	65 (56)
50–59	2 (1.8)	31 (26.7)
60–69	32 (28.6)	9 (7.8)
70–79	59 (52.7)	9 (7.8)
>80	16 (14.3)	2 (1.7)
Cold ischemia time (min)	478.58 (146.14)	482.58 (153.43)
Donor height (cm)	167.17 (10.1)	169.22 (11.17)
Donor race (%)		
White	112 (100)	116 (100)
Black	0 (0)	0 (0)
Cause of death		
Trauma	4 (3.6)	31 (26.8)
Stroke	105 (93.8)	73 (62.9)
Anoxia	3 (2.7)	7 (6.9)
Other	0 (0)	5 (45)
Non–heart-beating donor (%)	0 (0)	0 (0)
Split liver transplant (%)	0 (0)	0 (0)

Data expressed as mean (standard deviation) or frequency (%).

Table 3. Hepatic Hemodynamic Characteristics and ICG-PDR for Low and High-quality Grafts

	DRI >1.70 (n = 112)	DRI <1.70 (n = 116)	*P*
Hepatic artery flow (mL/min)	234.2 ± 121.35	287.24 ± 156.84	.02
Hepatic artery flow/ sLTV donor*100 g (mL/min*100 g)	15.1 ± 7.82	18.52 ± 10.47	.02
Portal vein flow (mL/min)	1518.79 ± 583.87	1556.79 ± 487.25	.48
Portal vein flow/sTLV donor* 100 g (mL/min*100 g)	99.14 ± 40.06	102.76 ± 39.49	.58
Total hepatic flow (mL/min)	1753.86 ± 606.59	1844 ± 518.34	.25
Total hepatic flow/ sTLV donor *100 g (mL/min*100 g)	114.4 ± 41.82	121.33 ± 43.08	.38
PDR-ICG at 60 min (%/min)	14.75 ± 6.52	16.68 ± 6.47	.09
PDR-ICG at day 1 (%/min)	15.31 ± 7.15	17.50 ± 8.08	.10

Data expressed as mean ± standard deviation.
Abbreviations: DRI, donor risk index; PDR-ICG, Intraoperative arterial hepatic flow and indocyanine green clearance; sTLV, standard total liver volume.

DISCUSSION

Numerical prediction models of short- and long-term survival have been developed in patients with liver transplantation. Most of these models include variables of the donor, recipient, and surgical procedure utilized [2,8–10]. The DRI, as described by Feng et al [3], and its validation within the Eurotransplant Registry (Eurotransplant DRI) [11] as a predictive model demonstrated the importance of donor factors on the final results of liver transplantation. It is necessary to analyze whether these predictive models of survival, based on donor characteristics, could identified high-risk grafts. These grafts are more likely to suffer early allograft disfunction or to have an impact on intraoperative liver hemodynamics, especially in those DRIs associated with worse outcomes. The 8 donor variables identified by Feng et al are associated with worse survival outcomes. When evaluated, these variables allow the organ liver transplant team to estimate the theoretical risk of any graft offered. This also allows for adequate donor-recipient pairing based on severity of the condition of the organ recipient. In the United States, the DRI has facilitated the analysis of donor quality and outcomes of transplanted organs. In an analysis of organ donations over the last 10 years, it was possible to verify a progressive increase in

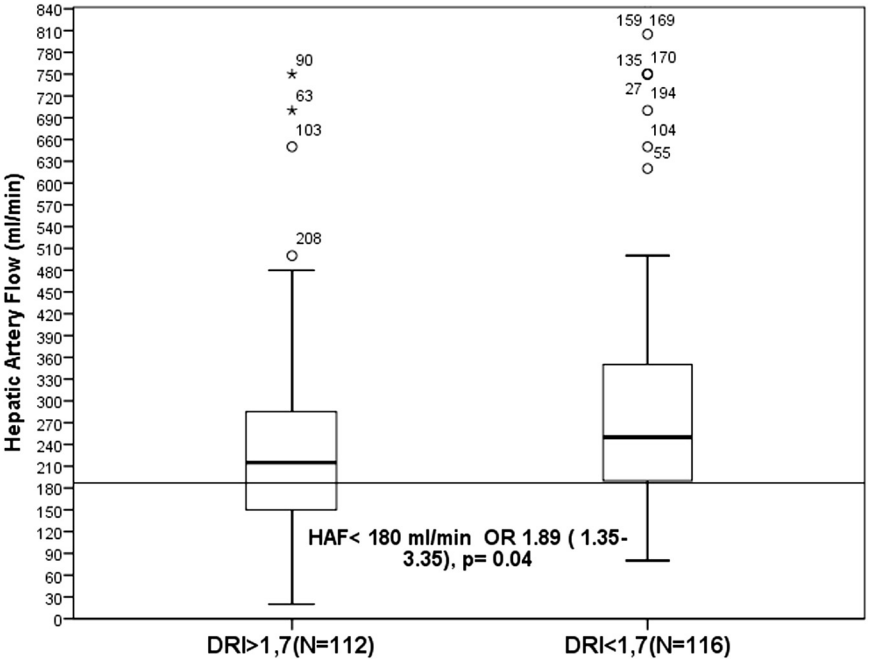

Fig 1. DRI and its relationship with HAF.

donations with cardiac death (DCD) and of elderly liver grafts, which corresponds to a progressive increase in DRI and poorer graft quality [12]. Over the last decade, the DRI has served as a useful model of donor quality and has helped us to realize how donor factors can impact recipients [13].

The impact of measurement of liver perfusion using a flowmeter was studied by Pratschke et al [6] and other investigators [14–16]. They concluded that impaired arterial blood flow after reperfusion represents a significant predictor of early allograft dysfunction (EAD) and is associated with impaired graft survival. Others have suggested an association between liver perfusion and development of arterial thrombosis [17]. Olmedilla et al suggested that indocyanine green clearance within the first day after LT could predict short-term survival and the need for retransplantation. Moreover, a risk score that included values $\geq$2.2 for international normalized ratio and <10%/min for ICG-PDR demonstrated negative predictive values of 94.12% [4,5].

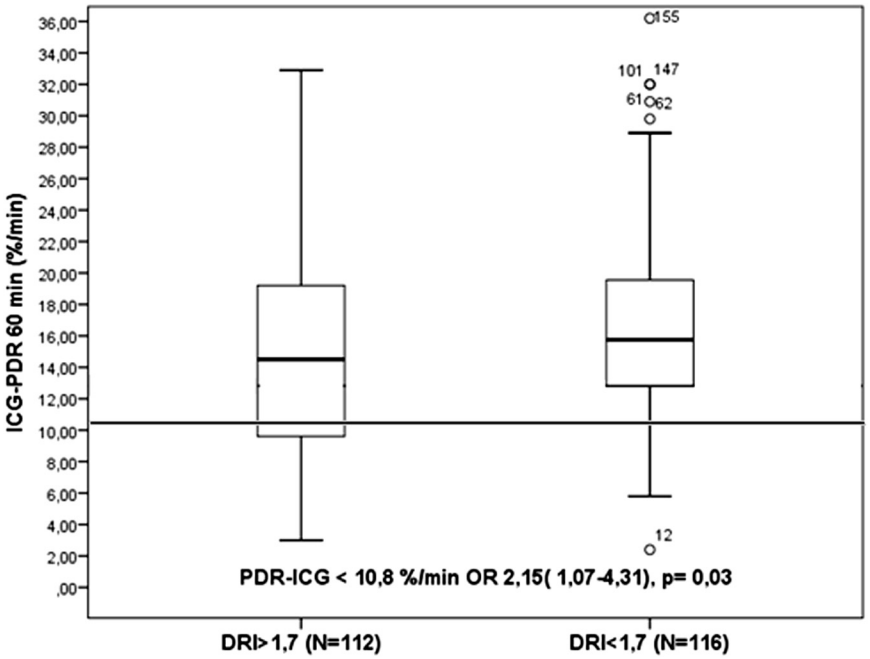

Fig 2. DRI and its relationship with ICG-PDR 60 min.

In our study 49.12% of the grafts (n = 112) had a DRI >1.70, and 50.88% (n = 116) lower than 1.70, which is the value of the DRI associated with an increase in the number of graft complications according to the literature [13,18]. We established the DRI cutpoint of 1.70, according to the previous literature, showing that patients with DRI >1.70 had an arterial flow of 234.2 ± 121.35 mL/min, as compared with patients with a DRI <1.70 who had an arterial flow of 287.24 ± 156.84 mL/min. These differences were statistically significant. Moreover, when HAF was adjusted by estimated donor liver volume, statistical significance was maintained. However, when portal vein flow (PVF) and total hepatic flow (THF) were analyzed in relation to the preoperative DRI score, no statistical significance was observed.

A DRI of >1.70 is considered indicative of a poor quality liver with worse results in terms of long-term survival. In our analysis, grafts with a DRI >1.70 were associated with a decrease in the HAF compared with those with a DRI <1.70. We are unaware of any study that linked DRI with HAF, so we can hypothesize that an elevated DRI is associated with a poorer graft. In our study, "poor quality grafts" are referred to as grafts of more advanced age and longer ischemia times, due to the absence of DCDs or split transplant procedures during this period. Those variables are known to produce hepatocyte and sinusoidal damage and to have a greater susceptibility to damage by ischemia-reperfusion. This can lead to increased IVR caused by a decrease in intraoperative HAF [19–22]. When we analyzed based on a HAF cutpoint of 180 mL/min, we found that grafts with a DRI >1.70 were twice as likely to have a HAF of <180 mL/min, with $P = .04$ (Fig 1). Currently, and thanks to advances in liver transplantation with reduced-size grafts, we can perform intraoperative maneuvers to modulate liver flow [23]. In whole graft liver transplantation, many authors have suggested performing maneuvers when the PVF is >1300 mL/min, such as a splenic artery ligation or splenectomy, depending on the case. Others suggested looking for splenorenal shunts if insufficient PVF is found intraoperatively, normally at <1000 mL/min [24,25]. In our experience, when we found a deficient HAF, normally <100 mL/min, we attempted to test the hepatic buffer response occluding the splenic artery. If we identified modifications in HAF we usually performed some maneuvers to modulate the liver flow. In those cases where we did not find modifications, we thought we were in the case of "resistant-to-flow" graft. If that was the case, we should be alert in the postoperative time to decide retransplantation if other conditions were present as EAD parameters, shock condition or decrease of ICG-PDR [26–28].

In early reperfusion after liver transplatation, ICG-PDR could be useful more as a measure of liver perfusion than liver synthesis. Otherwise, on the first postoperative day it could be a good predictor of poorer results related to liver function, as suggested by Olmedilla et al [4,5]. In our study, we showed a decrease in ICG-PDR at 60 minutes after reperfusion in those grafts with a DRI >1.70 (Fig 2). Poor quality grafts with an average score of 2.15 (1.07–4.31) are likely to have an ICG-PDR of <10.8%/min ($P = .03$). This is limited by the fact that we could not demonstrate whether poor quality grafts indicate worse liver synthesis or worse liver perfusion based on measurement of ICG-PDR.

Our study is not without limitations. First, graft steatosis was not evaluated in all grafts. Steatosis is well-known to be related to worse outcomes in liver transplantation, and could affect HAF and ICG-PDR findings. Graft biopsy data and the relationship with DRI were not analyzed, so we remain uncertain as to whether DRI was related to intrahepatic resistance, but we could suggest a relationship due to the low HAF and decrease in ICG-PDR seen in the poor quality grafts.

We know by the literature that an impairment in liver flow and decrease in ICG-PDR is related to worse outcomes in liver transplantation. We suggest that poor quality grafts are associated with decreases in those measurements. In the future, and with the new advances in liver machine perfusion, measurement of liver flow could be a useful tool to assess graft quality [29,30].

CONCLUSION

The DRI considers variables such as advanced age and cold ischemia time. Poor quality grafts have a greater susceptibility to ischemia-reperfusion damage. The measurement of a decreased intraoperative arterial flow may suggest an early increase in intrahepatic resistance.

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